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| 10/807,897 | 03/24/2004 | Rong Xiang | TSRI 874.1 | 6550 |

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| EXAMINER | |
|---|---|
| SHEN, WU CHENG WINSTON | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/807,897 | XIANG ET AL. | |
| | Examiner | Art Unit | |
| | Wu-Cheng Winston Shen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,26-29 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,26-29 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06/03/2004 and 03/24/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response received on 03/19/2007 has been entered. Claims 1, 26-29, and 53 are pending. Claims 2-25 and 30-52 have been cancelled.

Claims 1, 26, 28, and 53 have been amended.

Claim 1 has been amended to replace the phrase "cancer-associated Inhibitor of Apoptosis-family protein (IAP-family protein)" with the phrase "survivin protein", and to replace the phrase "immunoreactive gene product" with "cytokine". Applicant indicated that support for these amendments can be found in the specification, e.g., at page 8, lines 13-25; page 17, lines 5-11; and in examples 1-8 on pages 31-37, and examples 14-19 on pages 40-47.

Claim 26 has been amended to specify that the DNA construct encoding the survivin protein comprises elected SEQ ID NO: 3, and to delete the other sequences from the claim.

Claim 28 has been amended to specify that the DNA construct encoding the immunoreactive cytokine comprises elected SEQ ID NO: 7, and to delete the other sequences from the claim.

Claim 53 has been amended in accordance with the changes made in claim 1, in order to provide proper antecedent basis.

This application 10/807,897 filed on March 24, 2004 claims the benefit of 60/457,009 filed on 03/24/2003.

***Status of claims:*** Claims 1, 26-29, and 53 are currently under examination.

***Claim Objections***

1. Previous objection to claims 26 and 28 because of the following informalities: recitations of non-elected SEQ ID numbers, is ***withdrawn*** because claims 26 and 28 have been amended to only refer to the elected sequence numbers (i.e., SEQ ID NO: 3 and SEQ ID NO: 7, respectively).

***Claim Rejection - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Previous rejection of claims 1, 2, 26-29, and 51-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is ***withdrawn*** because claims 1, 26-29, and 53 have been amended.

More specifically, claim 1 has been amended to replace the phrase "cancer-associated Inhibitor of Apoptosis-family protein (lAP-family protein)" with the phrase "survivin protein", and to replace the phrase "immunoreactive gene product" with "cytokine". Applicant indicated that support for these amendments can be found in the specification, e.g., at page 8, lines 13-25; page 17, lines 5-11; and in examples 1-8 on pages 31-37, and examples 14-19 on pages 40-47.

Claim 26 has been amended to specify that the DNA construct encoding the survivin protein comprises elected SEQ ID NO: 3, and to delete the other sequences from the claim.

Claim 28 has been amended to specify that the DNA construct encoding the cytokine comprises elected SEQ ID NO: 7, and to delete the other sequences from the claim.

Claim 53 has been amended in accordance with the changes made in claim 1, in order to provide proper antecedent basis.

3. Claims 1, 26-29, and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA vaccine suitable for eliciting an immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier, **does not** reasonably provide enablement for the said method comprising *any cytokine*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. *This rejection is necessitated by the claim amendments of claim 1.*

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the

breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

The nature of the instant invention is to immunize a person with a DNA vaccine comprising a DNA construct encoding a survivin and a cytokine, wherein immune response directed to survivin present in cancer cells occurs in the person immunized with the DNA vaccine and the immune response is boosted by the cytokine. The breadth of the claims encompasses a DNA vaccine comprising a DNA construct encoding a survivin and any cytokine.

The specification disclosed preparation of a DNA vaccine encoding MuSurvivin and MuCCL21 (See, Example 14 of instant application) and oral vaccination and tumor challenge of mice with a vaccine of Example 14 (See Example 15 of instant application).

With regard to CCL21/SLC (secondary lymphoid tissue chemokine) as a cytokine that enhances T cell mediated immune response, Luther et al. teach the comparison of CCL19 transgenic mice with mice expressing CCL21 (secondary lymphoid tissue chemokine) revealed that CCL21 induced larger and more organized infiltrates. A more significant role for CCL21 is also suggested in lymphoid tissues, as CCL21 protein was found to be present in lymph nodes and spleen at much higher concentrations than CCL19. (See Abstract, Luther, Differing activities of homeostatic chemokines CCL19, CCL21, and CXCL12 in lymphocyte and dendritic cell recruitment and lymphoid neogenesis. *J Immunol.* 169(1): 424-33). Furthermore, **Cui et al.** demonstrated that intravascular plasmid DNA (pDNA) vaccine encoding herpes simplex virus type 1 (HSV-1) glycoprotein B (gB) effectively induces prophylactic immunity against lethal HSV-1 infection in mice. Cui et al. investigated whether the vaccine potency is further

improved by coadministration of cytokine genes together with a low dose of genetic vaccine. pDNA encoding certain cytokines was capable of elevating survival rates of HSV-1-infected mice when coinjected with 1 μg of gB pDNA, however, some cytokines, such as IL-10, failed to affect the effectiveness of the immunization (See Abstract, Cui et al., Cytokine genetic adjuvant facilitates prophylactic intravascular DNA vaccine against acute and latent herpes simplex virus infection in mice. *Gene Ther.* 12(2): 160-8, 2005). Therefore, not all cytokines are effective as adjuvants for increasing anti-tumor immune responses. Consistent with this notion, **Dieu et al.** indicated that DCs (dendritic cells) function as sentinels of the immune system. DCs traffic from the blood to the tissues where, while immature, they capture antigens. DCs then leave the tissues and move to the draining lymphoid organs where, converted into mature DC, they prime naive T cells. Significantly, Dieu et al. observed selective recruitment of immature and mature dendritic cells by distinct chemokines expressed in different anatomic sites (Dieu et al. Selective recruitment of immature and mature dendritic cells by distinct chemokines expressed in different anatomic sites. *J Exp Med.*, 188(2):373-86, 1998).

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the invention commensurate in scope with these claims 1, 26-29, and 53 of instant application.

***Claim Rejection - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Previous rejection of claims 1 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al. (Bennett et al. U.S. Patent No. 6,335,194 and WO200157059-A1), is withdrawn, is ***withdrawn*** because claims 1 and 26-29 have been amended.

More specifically, claim 1 has been amended to replace the phrase "cancer-associated Inhibitor of Apoptosis-family protein (lAP-family protein)" with the phrase "survivin protein", and to replace the phrase "immunoreactive gene product" with "cytokine". Applicant indicated that support for these amendments can be found in the specification, e.g., at page 8, lines 13-25; page 17, lines 5-11; and in examples 1-8 on pages 31-37, and examples 14-19 on pages 40-47.

Claim 26 has been amended to specify that the DNA construct encoding the survivin protein comprises elected SEQ ID NO: 3, and to delete the other sequences from the claim.

5. Previous rejection of claims 1 and 53 are rejected under 35 U.S.C. 102(e) as being anticipated by Girard et al. (US patent publication No. 2004/0224408, publication date Nov. 11, 2004), is ***withdrawn*** because claims 1 and 53 have been amended.

More specifically, claim 1 has been amended to replace the phrase "cancer-associated Inhibitor of Apoptosis-family protein (lAP-family protein)" with the phrase "survivin protein", and to replace the phrase "immunoreactive gene product" with "cytokine". Applicant indicated

that support for these amendments can be found in the specification, e.g., at page 8, lines 13-25; page 17, lines 5-11; and in examples 1-8 on pages 31-37, and examples 14-19 on pages 40-47.

Claim 53 has been amended in accordance with the changes made in claim 1, in order to provide proper antecedent basis.

***Claim Rejection - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Previous rejection of claims 1, 26, 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. (Bennett et al. U.S. Patent No. 6,335,194 and WO200157059-A1) taken with Pawelek et al. (U.S. patent 6,190,657, date of patent Feb. 20, 2001), is ***withdrawn*** because claims 1 and 26 have been amended.

More specifically, claim 1 has been amended to replace the phrase "cancer-associated Inhibitor of Apoptosis-family protein (lAP-family protein)" with the phrase "survivin protein", and to replace the phrase "immunoreactive gene product" with "cytokine". Applicant indicated that support for these amendments can be found in the specification, e.g., at page 8, lines 13-25; page 17, lines 5-11; and in examples 1-8 on pages 31-37, and examples 14-19 on pages 40-47.

Claim 26 has been amended to specify that the DNA construct encoding the survivin protein comprises elected SEQ ID NO: 3, and to delete the other sequences from the claim.

7. Previous rejection of claims 1 and 28 under 35 U.S.C. 103(a) as being unpatentable over Girard et al. (US patent publication No. 2004/0224408, publication date Nov. 11, 2004) taken with Tanabe et al. (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997), is ***withdrawn*** because claims 1 and 28 have been amended.

More specifically, claim 1 has been amended to replace the phrase "cancer-associated Inhibitor of Apoptosis-family protein (IAP-family protein)" with the phrase "survivin protein", and to replace the phrase "immunoreactive gene product" with "cytokine". Applicant indicated that support for these amendments can be found in the specification, e.g., at page 8, lines 13-25; page 17, lines 5-11; and in examples 1-8 on pages 31-37, and examples 14-19 on pages 40-47.

Claim 28 has been amended to specify that the DNA construct encoding the cytokine comprises elected SEQ ID NO: 7, and to delete the other sequences from the claim.

8. Claims 1, 26, 28 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Rovero et al.** (Rovero et al. Insertion of the DNA for the 163-171 peptide of IL1beta enables a DNA vaccine encoding p185(neu) to inhibit mammary carcinogenesis in Her-2/neu transgenic BALB/c mice. *Gene Ther.* 8(6): 447-52, 2001) taken with **Altieri** (Altieri, Validating survivin as a cancer therapeutic target. Nat Rev Cancer. 3(1): 46-54, 2003), **Nagira et al.** (Nigira et al., A lymphocyte-specific CC chemokine, secondary lymphoid tissue chemokine (SLC), is a highly

efficient chemoattractant for B cells and activated T cells. *Eur J Immunol.* 28(5):1516-23, 1998), **Bennett et al.** (Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55; this reference has been provided in the Non-Final office action mailed on 12/13/2006), **Tanabe et al.** (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, direct submission of DNA sequences of CCL21; this reference has been provided in the Non-Final office action mailed on 12/13/2006. *This rejection is necessitated by the claim amendments of claim 1.*

Claim 1 reads on a DNA vaccine suitable for eliciting an immune response against comprising a DNA construct operable encoding at least one survivin protein and at least one cytokine.

With regard to immune response against a tumor antigen and boosted by a genetic cytokine adjuvant, Rovero *et al.* taught use of DNA vaccination against tumor antigens in combination with a cytokine. **Rovero et al.** teach an assessment of the effectiveness of DNA vaccination in prevention of the mammary adenocarcinomas of BALB/c female mice transgenic for the activated rat Her-2/neu oncogene, a breast cancer specific tumor antigen (See Abstract, page 447, Rovero et al., 2001). Rovero et al. also teach that an enhancement of the potency of DNA vaccines has been sought through the employment of cytokines as adjuvants, and vaccines encoding antigens fused with immunological molecules and cytokines elicit more effective responses and the ability of cytokines to enhance the immune recognition of tumor antigens has been extensively exploited. More specifically, Rovero et al. compared the ability of DNA vaccination with plasmids coding for the extracellular domain of product of rat Her-2/neu

($p185^{neu}$) alone (ECD) or fused with the DNA coding for this IL-1β peptide (ECD-IL-1βp) to block the progression of Her-2/neu carcinogenesis in female BALB/c mice transgenic for the activated rat Her-2/neu oncogene under the control of the MMTV promoter (BALB-neuT). Rovero et al. reported that all the mammary glands of these mice independently undergo a very aggressive carcinogenesis that mirrors some features of the formation of lobular carcinoma in women. Vaccination with plasmids coding for ECD alone did not block this carcinogenesis, whereas vaccination with ECD-IL-1βp was followed by a significant delay (See Introduction, page 447, Rovero et al., 2001).

Rovero et al. does not teach **(i)** use of a DNA construct encoding survivin or SEQ ID NO:3 (survivin protein sequence) as a tumor specific antigen and as a cancer therapeutic target, or **(ii)** CCL21/SLC (secondary lymphoid tissue chemokine) as a cytokine that enhance T cells mediated immune response or a nucleic acid encoding such as represented by SEQ ID NO:7.

**(i)** With regard to survivin being a tumor specific antigen and as a cancer therapeutic target, **Altieri** reviewed the validation of survivin as a cancer therapeutic target. Altieri teaches that Survivin expression is undetectable in most normal adult tissues, but is overexpressed in virtually every human tumor that has been studied. Several mechanisms have been proposed to account for this overexpression, one of which is loss of wild-type p53. Altieri further teaches that in mammalian cells, apoptosis is modulated by two protein families: the BCL2 (which, like HER2, is involved in regulation and development of breast cancer) and inhibitor of apoptosis (IAP) families. Survivin is a unique member of the IAP family and is associated with several subcellular compartments and many signaling pathways regulate its expression.

Altieri indicated that the two main reasons for considering survivin as an attractive therapeutic target in cancer are its differential expression in tumors versus normal tissues, and its potential requirement for maintaining cancer-cell viability. A survivin-based therapy would be expected to carry limited toxicity for normal tissues and to be effective at removing general cell-viability machinery that is exploited by cancer cells. A promising therapeutic approach to target survivin relied on the ability to generate an antigen-specific immune response against survivin-bearing tumor cells (Fig. 5a, Altieri, 2002). Altieri indicated that several groups have independently validated this hypothesis by the observation that T cells mount a vigorous cytolytic response against survivin peptides *in vitro* and *in vivo*, and that HLA class I-restricted cytolytitic T cells against survivin peptides exist in patients with breast cancer, leukaemia and melanoma *in vivo*. Altieri concluded that these data indicate that a cancer-specific immune response to survivin might be used for potential vaccination strategies, with the advantage of minimizing the risks of autoimmune effects (See bridging paragraph, pages 50-51; Altieri, 2002).

With regard to DNA construct encoding a murine survivin protein comprising SEQ ID No. 3 (claim 26), **Bennett et al.** teach DNA encoding mouse survivin that identical to SEQ ID NO: 3 (See Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55, detailed alignment of sequences listed below)

```
RESULT 1

AAS21530
ID   AAS21530 standard; cDNA; 955 BP.
XX
AC   AAS21530;
XX
DT   21-NOV-2001  (first entry)
XX
DE   DNA encoding mouse survivin.
XX
KW   Survivin; human; mouse; cytostatic; antisense oligonucleotide;
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KW hyperproliferative condition; cancer; apoptosis; cytokinesis; ss.
XX
OS Mus musculus.
XX
PN WO200157059-A1.
XX
PD 09-AUG-2001.
XX
PF 30-JAN-2001; 2001WO-US002939.
XX
PR 02-FEB-2000; 2000US-00496694.
XX
PA (ISIS-) ISIS PHARM INC.
XX
PI Bennett CF, Ackermann EJ, Swayze EE, Cowsert LM;
XX
DR WPI; 2001-488863/53.
XX
PT Novel antisense compounds for modulating the expression of Survivin and
PT treatment of cancer.
XX
PS Example 13; Page 80-81; 120pp; English.
XX
CC The invention relates to antisense oligonucleotides targeted to a nucleic
CC acid molecule encoding human Survivin, where the antisense
CC oligonucleotide inhibits the expression of human Survivin. These
CC antisense oligonucleotides are used in the treatment of an animal
CC suffering from a disease or condition associated with Survivin, e.g. a
CC hyperproliferative condition such as cancer, and comprises administering
CC a therapeutically or prophylactically effective amount of the antisense
CC oligonucleotide so that expression of Survivin is inhibited. The
CC oligonucleotides can also be used to treat a human suffering from a
CC disease or condition characterised by a reduction in apoptosis comprising
CC administering the antisense oligonucleotide to a human. In addition, the
CC antisense oligonucleotide and a cytotoxic chemotherapeutic agent e.g.
CC taxol or cisplatin, can be used to modulate apoptosis, cytokinesis or the
CC cell cycle, or inhibit the proliferation in a cancer cell by contacting
CC the cell with the antisense oligonucleotide. AAS21521-AAS21768 represent
CC Survivin nucleic acids, and antisense oligonucleotides targeted to
CC Survivin, used in the method of the invention
XX
SQ Sequence 955 BP; 230 A; 227 C; 265 G; 233 T; 0 U; 0 Other;

Query Match 100.0%; Score 955; DB 5; Length 955;
Best Local Similarity 100.0%; Pred. No. 3.6e-284;
Matches 955; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 GGCACGAGGGGGCCGGGGCTCTCCCGGCATGCTCTGCGGCGCGCCTCCGCCCGCGCGATT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GGCACGAGGGGGCCGGGGCTCTCCCGGCATGCTCTGCGGCGCGCCTCCGCCCGCGCGATT 60

Qy         61 TGAATCCTGCGTTTGAGTCGTCTTGGCGGAGGTTGTGGTGACGCCATCATGGGAGCTCCG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db        61 TGAATCCTGCGTTTGAGTCGTCTTGGCGGAGGTTGTGGTGACGCCATCATGGGAGCTCCG 120

Qy       121 GCGCTGCCCCAGATCTGGCAGCTGTACCTCAAGAACTACCGCATCGCCACCTTCAAGAAC 180
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       121 GCGCTGCCCCAGATCTGGCAGCTGTACCTCAAGAACTACCGCATCGCCACCTTCAAGAAC 180

Qy       181 TGGCCCTTCCTGGAGGACTGCGCCTGCACCCCAGAGCGAATGGCGGAGGCTGGCTTCATC 240
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       181 TGGCCCTTCCTGGAGGACTGCGCCTGCACCCCAGAGCGAATGGCGGAGGCTGGCTTCATC 240

Qy       241 CACTGCCCTACCGAGAACGAGCCTGATTTGGCCCAGTGTTTTTTCTGCTTTAAGGAATTG 300
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       241 CACTGCCCTACCGAGAACGAGCCTGATTTGGCCCAGTGTTTTTTCTGCTTTAAGGAATTG 300

Qy       301 GAAGGCTGGGAACCCGATGACAACCCGATAGAGGAGCATAGAAAGCACTCCCCTGGCTGC 360
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       301 GAAGGCTGGGAACCCGATGACAACCCGATAGAGGAGCATAGAAAGCACTCCCCTGGCTGC 360

Qy       361 GCCTTCCTCACTGTCAAGAAGCAGATGGAAGAACTAACCGTCAGTGAATTCTTGAAACTG 420
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       361 GCCTTCCTCACTGTCAAGAAGCAGATGGAAGAACTAACCGTCAGTGAATTCTTGAAACTG 420

Qy       421 GACAGACAGAGAGCCAAGAACAAAATTGCAAAGGAGACCAACAACAAGCAAAAAGAGTTT 480
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       421 GACAGACAGAGAGCCAAGAACAAAATTGCAAAGGAGACCAACAACAAGCAAAAAGAGTTT 480

Qy       481 GAAGAGACTGCAAAGACTACCCGTCAGTCAATTGAGCAGCTGGCTGCCTAATGCTGAGCC 540
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       481 GAAGAGACTGCAAAGACTACCCGTCAGTCAATTGAGCAGCTGGCTGCCTAATGCTGAGCC 540

Qy       541 TTTGCTGAGATAACTTGGACCTGAGTGACATGCCACATCTAAGCCACGCATCCCAGCTTT 600
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       541 TTTGCTGAGATAACTTGGACCTGAGTGACATGCCACATCTAAGCCACGCATCCCAGCTTT 600

Qy       601 TCCAGCCAGGGCCTCCTAGCAGGATCTTAGAGAAGGAGACAGTGGTATTTTGAAACTGGA 660
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       601 TCCAGCCAGGGCCTCCTAGCAGGATCTTAGAGAAGGAGACAGTGGTATTTTGAAACTGGA 660

Qy       661 TATCAAATATTTTTGGTTTTGCTTTAAAGTGGCTACCTCTCTTTGGTTTTGTGGCTTTGC 720
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       661 TATCAAATATTTTTGGTTTTGCTTTAAAGTGGCTACCTCTCTTTGGTTTTGTGGCTTTGC 720

Qy       721 TCTATTGTGACGTGGACTTAAGCAATAAGGAAGTGATGAAGGGACAGTGTTCTCTGACAG 780
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       721 TCTATTGTGACGTGGACTTAAGCAATAAGGAAGTGATGAAGGGACAGTGTTCTCTGACAG 780

Qy       781 GACCTGTGGGGGTCGGGGTGCCTGTGCAAGGTCTTGGTTCTGATTGTGATATTTCCATAC 840
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       781 GACCTGTGGGGGTCGGGGTGCCTGTGCAAGGTCTTGGTTCTGATTGTGATATTTCCATAC 840

Qy       841 AGGGCTGCTAATGCAGCCCATGGGTAAGTGTGGTTATATGTGTTTGTGCTGATAATTTTG 900
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       841 AGGGCTGCTAATGCAGCCCATGGGTAAGTGTGGTTATATGTGTTTGTGCTGATAATTTTG 900
```

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Qy        901 TCCTGATGAGTTTTCCTACCACGGGGTAACGGAATAAAATCACTTGAAAAAGTGG 955
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 TCCTGATGAGTTTTCCTACCACGGGGTAACGGAATAAAATCACTTGAAAAAGTGG 955
```

**(ii)** Claim 28 reads on SEQ No: 7, which is a murine CCL21, which is also known as SLC (secondary lymphoid tissue chemokine). With regard to CCL21/SLC (secondary lymphoid tissue chemokine; SEQ ID NO:7) as a cytokine that enhances T cell mediated immune response, Nagira et al. teach that secondary lymphoid tissue chemokine (SLC) is a CC chemokine expressed mainly in lymph nodes, appendix and spleen, and specifically chemotactic for lymphocytes (Nagira et al., J. Biol. Chem. 1997. 272: 19518-19524). Nagira et al. carried out transendothelial migration assays to determine the classes and subsets of lymphocytes migrating toward SLC. SLC attracted freshly isolated B cells with high efficiency and T cells modestly. Thus, Nagira et al. show that SLC is the first CC chemokine with a strong chemotactic activity on fresh B cells. Among T cell types and subsets, Nagira et al. show that SLC broadly attracted $CD4^+$ and $CD8^+$ cells, $CD45RO^-$ (naive) and $CD45RO^+$ (memory) cells, and $CD26^{high}$ (activated) and $CD26^{low-}$ (resting) cells. Nagira et al. further show that SLC also attracted both L-$selectin^+$ and L-$selectin^-$ subpopulations of various T cell subsets and B cells (See Abstract, Nigira et al., A lymphocyte-specific CC chemokine, secondary lymphoid tissue chemokine (SLC), is a highly efficient chemoattractant for B cells and activated T cells. *Eur J Immunol.* 28(5):1516-23, 1998).

With regard to DNA construct encodes a murine CCL21 cytokine comprises SEQ ID NO: 7 (claim 53), **Tanabe et al.** teach DNA encoding mouse CCL21 that is identical SEQ ID NO: 7 (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park

Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, detailed alignment of sequences listed below; this reference has been provided in the Non-Final office action mailed on 12/13/2006).

```
RESULT 1
AF006637
LOCUS       AF006637                615 bp    mRNA    linear   ROD 22-JUN-
1997
DEFINITION  Mus musculus beta-chemokine TCA4 mRNA, complete cds.
ACCESSION   AF006637
VERSION     AF006637.1  GI:2209188
KEYWORDS    .
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia;
            Sciurognathi; Muroidea; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 615)
  AUTHORS   Tanabe,S., Lu,Z., Luo,Y., Quackenbush,E.J., Berman,M.A.,
            Collins-Racie,L.A., Mi,S., Reilly,C., Lo,D., Jacobs,K.A. and
            Dorf,M.E.
  TITLE     Direct Submission
  JOURNAL   Submitted (03-JUN-1997) Genetics Institute, 87 Cambridge Park
            Drive, Cambridge, MA 02140, USA
FEATURES             Location/Qualifiers
     source          1. .615
                     /organism="Mus musculus"
                     /mol_type="mRNA"
                     /db_xref="taxon:10090"
                     /tissue_type="thymus"
                     /dev_stage="adult"
     CDS             97. .498
                     /note="beta-chemokine"
                     /codon_start=1
                     /product="TCA4"
                     /protein_id="AAB61440.1"
                     /db_xref="GI:2209189"

/translation="MAQMMTLSLLSLVLALCIPWTQGSDGGGQDCCLKYSQKKIPYSI

VRGYRKQEPSLGCPIPAILFSPRKHSKPELCANPEEGWVQNLMRRLDQPPAPGKQSPG
                    CRKNRGTSKSGKKGKGSKGCKRTEQTQPSRG"
ORIGIN

  Query Match             100.0%;  Score 615;  DB 6;  Length 615;
  Best Local Similarity   100.0%;  Pred. No. 3e-193;
  Matches  615;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 GAATTCGGCCAAAGAGGCCTACGGCCAAAGAGGGCTAAACTTGCGGCTGTCCATCTCACC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GAATTCGGCCAAAGAGGCCTACGGCCAAAGAGGGCTAAACTTGCGGCTGTCCATCTCACC 60
```

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Qy        61 TACAGCTCTGGTCTCATCCTCAACTCAACCACAATCATGGCTCAGATGATGACTCTGAGC 120
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        61 TACAGCTCTGGTCTCATCCTCAACTCAACCACAATCATGGCTCAGATGATGACTCTGAGC 120

Qy       121 CTCCTTAGCCTGGTCCTGGCTCTCTGCATCCCCTGGACCCAAGGCAGTGATGGAGGGGGT 180
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       121 CTCCTTAGCCTGGTCCTGGCTCTCTGCATCCCCTGGACCCAAGGCAGTGATGGAGGGGGT 180

Qy       181 CAGGACTGCTGCCTTAAGTACAGCCAGAAGAAAATTCCCTACAGTATTGTCCGAGGCTAT 240
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       181 CAGGACTGCTGCCTTAAGTACAGCCAGAAGAAAATTCCCTACAGTATTGTCCGAGGCTAT 240

Qy       241 AGGAAGCAAGAACCAAGTTTAGGCTGTCCCATCCCGGCAATCCTGTTCTCACCCCGGAAG 300
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       241 AGGAAGCAAGAACCAAGTTTAGGCTGTCCCATCCCGGCAATCCTGTTCTCACCCCGGAAG 300

Qy       301 CACTCTAAGCCTGAGCTATGTGCAAACCCTGAGGAAGGCTGGGTGCAGAACCTGATGCGC 360
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       301 CACTCTAAGCCTGAGCTATGTGCAAACCCTGAGGAAGGCTGGGTGCAGAACCTGATGCGC 360

Qy       361 CGCCTGGACCAGCCTCCAGCCCCAGGGAAACAAAGCCCCGGCTGCAGGAAGAACCGGGGA 420
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       361 CGCCTGGACCAGCCTCCAGCCCCAGGGAAACAAAGCCCCGGCTGCAGGAAGAACCGGGGA 420

Qy       421 ACCTCTAAGTCTGGAAAGAAAGGAAAGGGCTCCAAGGGCTGCAAGAGAACTGAACAGACA 480
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       421 ACCTCTAAGTCTGGAAAGAAAGGAAAGGGCTCCAAGGGCTGCAAGAGAACTGAACAGACA 480

Qy       481 CAGCCCTCAAGAGGATAGCCCAGTAGCCCGCCTGGAGCCCAGGAGATCCCCCACGAACTT 540
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       481 CAGCCCTCAAGAGGATAGCCCAGTAGCCCGCCTGGAGCCCAGGAGATCCCCCACGAACTT 540

Qy       541 CAAGCTGGGTGGTTCACGGTCCAACTCACAGGCAAAGAGGGAGCTAGAAAACAGACTCAG 600
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       541 CAAGCTGGGTGGTTCACGGTCCAACTCACAGGCAAAGAGGGAGCTAGAAAACAGACTCAG 600

Qy       601 GAGCCGCTAGTCGAG 615
             |||||||||||||||
Db       601 GAGCCGCTAGTCGAG 615
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Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to modify the DNA vaccination construct encodes the extracellular domain of product of rat Her-2/neu ($p185^{neu}$) in combination with the cytokine IL-1β peptide, taught by Rovero et al, by replacing the breast tumor specific antigen Her-2/neu ($p185^{neu}$) with

non-breast cancer restricted tumor specific antigen survivin, taught by Altieri and Bennett et al., and by replacing DNA encodes cytokine IL-1β peptide taught by Rovero with DNA encoding cytokine CCL21, as taught by Luther et al. and Tanabe et al., and incorporate the DNA construct encodes both survivin and CCL21, which to achieve eliciting immune responses against various human cancer cells (and other mammalian cancer cells due to conservation of survivin in mammals) via both activation of B cell mediated production of antibody against survivin, which is highly expressed in virtually all human tumor cells, and T cell mediated cytolytic response enhanced by cytokine CCL21 directed immune response in a tumor cell specific mannerOne having ordinary skill in the art would have been motivated to replacing the breast tumor specific antigen Her-2/neu ($p185^{neu}$) with non-breast cancer restricted tumor specific antigen survivin, taught by Altieri and Bennett et al., and by replacing DNA encodes cytokine IL-1β peptide with DNA encodes cytokine CCL21/SLC, as taught by Nagira et al. and Tanabe et al., because (i) survivin is highly expressed in virtually all human tumors, (ii) CCL21/SLC can enhance immune response against tumor specific antigen via both activation of T cells and attraction of B cells that produce antibody against survivin, which is highly expressed in virtually all human tumor cells, and T cell mediated cytolytic response and B cell mediated immune response enhanced by cytokine CCL21 directed immune response in a tumor cell specific manner.

There would have been a reasonable expectation of success given (i) successful DNA vaccine construct encodes both Her2 and IL-1β in eliciting immune responses to breast cancer specific tumor antigen Her2 by the teachings of Rovero et al., and (ii) successful validation of tumor specific antigen surviving as a cancer therapeutic target, by the teachings of Altieri and Bennett et al., (iii) successful demonstration of the effect of CCL21 in increasing T cell mediated

cytolytic response as well as B cell recruitment, by the teachings of Nagira et al. and Tanabe et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

9. Claims 1 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Rovero et al.** (Rovero et al. Insertion of the DNA for the 163-171 peptide of IL1beta enables a DNA vaccine encoding p185(neu) to inhibit mammary carcinogenesis in Her-2/neu transgenic BALB/c mice. *Gene Ther.* 8(6): 447-52, 2001) taken with **Altieri** (Altieri, Validating survivin as a cancer therapeutic target. Nat Rev Cancer. 3(1): 46-54, 2003), **Nagira et al.** (Nigira et al., A lymphocyte-specific CC chemokine, secondary lymphoid tissue chemokine (SLC), is a highly efficient chemoattractant for B cells and activated T cells. *Eur J Immunol.* 28(5):1516-23, 1998), **Bennett et al.** (Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55; this reference has been provided in the Non-Final office action mailed on 12/13/2006), **Tanabe et al.** (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, direct submission of DNA sequences of CCL21; this reference has been provided in the Non-Final office action mailed on 12/13/2006), and **Pawelek et al.** (Pawelek et al., U.S. patent 6,190,657, date of patent Feb. 20, 2001; this reference has been provided in the Non-Final office action mailed on 12/13/2006). *This rejection is necessitated by the claim amendments of claim 1.*

The teachings of Rovero et al., Altieri, Nagira et al., Bennett et al., and Tanabe et al. are as set forth in the preceding rejection under 35 U.S.C. 103(a). Rovero et al., Altieri, Nagira et

al., Bennett et al., and Tanabe et al. do not teach attenuated strains of *Salmonella typhimurium* as vectors for delivery of DNA construct.

With regard to using attenuated strains of *Salmonella typhimurium* as vectors for delivery of DNA construct, **Pawelek et al.** (U.S. patent 6,190,657, date of patent Feb. 20, 2001) teach the isolation and use of super-infective, tumor-specific, attenuated strains of parasites including, but not limited to, bacteria, fungi and parasites. In certain embodiments the parasites include the bacterium *Salmonella* spp., such as *Salmonella typhimurium*, the bacterium *Mycobacterium avium*, and the protozoan *Leishmania amazonensis*, for the diagnosis and treatment of sarcomas, carcinomas, and other solid tumor cancers. In other embodiments, the present invention is concerned with the isolation and use of super-infective, tumor-specific, suicide gene-containing strains of parasites (See Filed of Invention, column 1).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the DNA vaccine construct, based on the combined teachings of Rovero et al., Altieri, Nagira et al., Bennett et al., and Tanabe et al. encoding both survivin and CCL21, in an attenuated *Salmonella typhimurium* as DNA delivery vehicle, which has targeting selectivity for tumor cells, as taught by Pawelek et al.

One having ordinary skill in the art would have been motivated to use attenuated *Salmonella typhimurium* as DNA delivery vehicle because *Salmonella typhimurium* as DNA delivery vehicle is super-infective, tumor-specific, to achieve eliciting immune responses against various human cancer cells (and other mammalian cancer cells due to conservation of survivin in mammals) via both activation of B cell mediated production of antibody against survivin, which is highly expressed in virtually all human tumor cells, and T cell mediated cytolytic response

enhanced by cytokine CCL21 directed immune response in a tumor cell specific manner using super-infective, tumor-specific, attenuated *Salmonella typhimurium* as DNA delivery vehicle.

There would have been a reasonable expectation of success given (i) successful DNA vaccine construct encodes both Her2 and IL-1β in eliciting immune responses to breast cancer specific tumor antigen Her2 by the teachings of Rovero et al., and (ii) successful validation of tumor specific antigen surviving as a cancer therapeutic target, by the teachings of Altieri and Bennett et al., (iii) successful demonstration of the effect of CCL21 in increasing T cell mediated cytolytic response as well as chemo-attraction for B cells by CCL21, by the teachings of Nagira et al. and Tanabe et al. (iv) successful isolation and use of super-infective, tumor-specific, attenuated *Salmonella typhimurium* as DNA delivery vehicle, by the teachings of Pawelek et al. Additionally, the disclosure by instant application also echoes a reasonable expectation of success by the statement "When a patient is orally vaccinated with the transformed *Salmonella*, the bacteria are transported to Peyer's patches in the gut (i.e., secondary lymphoid tissues), which then stimulate an immune response (See last sentence, paragraph [0013], page 2 of instant application).

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

***Conclusion***

10. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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